PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MMV/PB60643	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2004/004242	International filing date *(day/month/year)* 20.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or national classification and IPC C07D471/16, A61K31/4985, A61P3/04, A61P25/32, A61P25/34, A61P29/00		
Applicant SB PHARMCO PUERTO RICO INC et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.08.2005	28.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Papathoma, S Telephone No. +49 89 2399-7536

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/004242

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-28 as originally filed

   Claims, Numbers

   1-24 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/004242

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-24

because:

☒ the said international application, or the said claims Nos. 18-24 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-B1-6 348 466 (HADDACH MUSTAPHA ET AL) 19 February 2002 (2002-02-19)

D2: WO 00/27850 A (NEUROCRINE BIOSCIENCES, INC; HADDACH, MUSTAPHA; GUO, ZHIQIANG; MCCARTH) 18 May 2000 (2000-05-18)

The application refers to CRF receptor antagonists of the formula (I).

1) Article 33(2) PCT

Structurally close related CRF receptor antagonists are disclosed in documents D1 and D2. Although in both of these documents the Ar-substituent can be further substituted by a piperidine ring (see claim 1 in both cases), this type of substitution was not explicitly disclosed in any of the examples.

The present subject-matter can therefore be considered as formally novel according to Article 33(2) PCT.

2) Article 33(3) PCT

The problem outlined in the present application is to provide compounds useful as CRF receptor antagonists. As the prior art (documents D1 and D2) has already dealt with this problem, the actual technical problem may be seen in the provision of **further** compounds as CRF receptor antagonists.

Alternative solutions to a known technical problem can be considered as inventive when it can be shown that they do not derive from the prior art in an obvious manner and that they indeed solve the problem eventually showing an unexpected effect.

With respect to the question whether the subject matter of the present application provides a "real" solution to the technical problem mentioned above, no biological tests are provided in the present application which could support that the disclosed examples do have the claimed activity.

With respect to the information given from the prior art and the question whether the solution provided by the present application can be derived in an obvious manner, this Authority considers the claimed compounds as structurally close related to the entities disclosed in the prior art, and that the modification, which distinguishes them from the latter can be regarded as part of the synthetic routine of the person skilled in the art when looking for alternative solutions.
As mentioned above, the present subject-matter differs form the prior art only in the further substitution of the Ar-substituent with an heterocyclic group. However, the prior art has already explicitly disclosed in claim 1 the piperidinyl substitution of the Ar-substituent.
For that reason, the present subject-matter is considered as not to involve inventive ingenuity, and therefore does not fulfill the requirements of Article 33(3) PCT.

An inventive merit could only be acknowledged in the case that the claimed subject matter shows unexpected effects with respect to the prior art.
Consequently, for a possible reconsideration regarding the evaluation of the inventive merit of the subject matter of the present application, further evidence will be needed, where the properties of the claimed compounds are compared with those of the structurally more related compounds from D1 / D2.

3) Article 34(4)(a)(I) PCT
For the assessment of the present claims 18-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1) The term "prodrug" mentioned in the description and in the claims leads to an unclear scope, since it is unclear which structures are intended.
The expression "prodrug" includes compounds obtained from another compound by a chemical reaction (structures which are structurally remote from the starting material), functional derivatives (compounds wherein the heteroatoms are exchanged by alternative atoms), compounds with numerous different types of side groups etc. Further it is an attempt to define the subject-matter in terms of the result to be achieved.
Therefore, such a formulation is not allowable.
Furthermore, prodrugs of the presently claimed compounds may well represent a completely separate invention from that disclosed in the present application and as such they are insufficiently disclosed according to Article 5 PCT, since the skilled person would not be able to produce all of these compounds without exercising an inventive step in accordance with Article 33(3) PCT.

2) The insufficient definition of the heterocycle (Het) of claim 1 leads to a broad and unclear scope, since it is unclear which structures are intended.
The applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/examples as being essential features of the invention described must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved **should be solved by the whole scope of the claimed subject matter** (every compound falling within its scope) and not just by individual compounds - especially since the problem may be seen in the provision of compounds acting on a biological system (i.e. on a system depending upon very different parameters). If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention.